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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,172	05/01/2001	Gregory G. Burrows	2357-003-03	5303

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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/847,172	BURROWS ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-40,54 and 59-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-40,54 and 59-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/200942 and is a continuation-in-part of U.S. Application Serial Number 09/153,586, which claims the benefit of the filing date of provisional application 60/064,552 and 60/064,555.

Claims 1-36, 41-53 and 55-58 have been canceled.

Claims 37-40, 54 and 59-82 are currently pending.

In view of Applicant's arguments filed October 17, 2006, the following new ground of rejection has been necessitated.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 37-40, 54, and 59-82 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible or specific asserted utility or a well established utility.

It was previously stated: "Briefly, the claims are broadly drawn to a method for reducing an immune response in a subject [claims 37-40, 69-80] and treating a disease caused by antigen-specific T cells [claims 54, 59-68, 81-82]. All claims require the administration to a subject a composition comprising an MHC class II construct having an $\alpha 1$ domain and a $\beta 1$ domain, but lacking an $\alpha 2$ domain and a $\beta 2$ domain. The claims are drawn to the in vivo treatment of an immune response including (and specifically reciting in claims 59-61 and 69-71) various autoimmune diseases characterized by different disease etiologies and reactivities to various autoantigens. The claims have been amended to recite that the immune response being treated in the subject is an "epitope-specific immune response." However, given the nature of the immune response in an autoimmune disease, the artisan would question the utility of treating the subject for an immune response against a single epitope. The typical autoimmune subject is reactive with a variety of epitopes even on a single antigen. For example, in myasthenia gravis it has been established that about 60-70% of the autoantibodies that bind to the nicotinic acetylcholine receptor (AChR) bind to a domain on the alpha subunit known as the "main immunogenic region" (MIR). However, even this MIR-directed population is heterologous, recognizing multiple epitopes within the MIR (page 2343, column 2 of Tzartos et al. (J. Immunol. [1985] 134(4):2343-2349; V on form PTO-892, newly cited) for example). Furthermore, this leaves 30-40% of those endogenous anti-AChR to bind to undetermined immunoepitopes. While the instant claims are drawn to the use of MHC-bound epitopes versus antibody epitopes, the reference is applicable because the subject is also reactive with a variety of MHC epitopes. Equally applicable to the utlility of the invention as presently claimed, Applicant is reminded that the effectiveness of treating a response to an autoantigen is dependent on several factors, the most critical of which is whether the therapy can be used to treat an ongoing autoimmune response or

whether it is only effective prophylactically (Tisch et al, Proc. Nat. Acad. Sci. (USA). [1994] 91:437-438; U on form PTO-892 of record, page 437, column 2, last paragraph in particular). Typically, an autoimmune disease is diagnosed only after significant tissue damage has already occurred. Administration of antigen after pathogenic T cells have been activated may have an exacerbating effect on the disease, rather than a tolerogenic one. Another problem during the treatment of autoimmune diseases is determinant spreading during the course of the disease. The Tisch et al reference also teaches that "the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM, and RA, in which there are responses to several autoantigens [...] and the critical inciting autoantigen(s) is not known" (page 437, third full paragraph of column 3 in particular). Treating a subject with a single epitope for treating an "epitope-specific immune response" therefore lacks utility because the treatment of that single response in a subject with an ongoing immune condition does not address epitope spreading and may exacerbate the subject's overall condition. The specification demonstrates only that the MHC peptides and antigenic determinants of the invention were capable of stimulating T cell lines and T cells derived from the peripheral blood lymphocytes of human subjects wherein the T cells were selected to be specific for the antigenic determinant. The specification does not show that the peptides disclosed in the specification were able to inhibit the autoimmune reactivity of any T cells, either those of T cell lines or patient-derived."

Applicant's arguments filed October 17, 2006 have been fully considered but they are not persuasive.

Applicant argues that the invention has utility because the claimed method does not need to be successful in all patients to be considered useful and effective. Applicant points to the anti-cancer antibody HERCEPTIN, which is approved for use despite only being effective in only 14% of patients for the treatment of metastatic breast cancer patients. This analogy is off-point, as administration of HERCEPTIN is not geared to the blocking/elimination of self reactive cells, rather the aim of HERCEPTIN treatment is the elimination of malignant breast tissue cells bearing the HER2 antigen.

The instant specification and the instantly claimed invention are drawn to administration of a modified MHC class II molecule bearing an antigenic molecule that is an epitope recognized by a T cell subset in order to affect T cells specific for the epitope. The aim disclosed in the present specification is to down-regulate the T cell response to the epitope, not to eliminate malignant cells. epitope spreading is not a concern when treating breast cancer patients with HERCEPTIN, however, due to the danger recognized in the art of exacerbating the patient's condition, epitope spreading is a concern when treating a T cell mediated disease, such as an autoimmune disease. The sole exemplification in the present specification is the treatment of EAE in Lewis rats with the major antigenic epitope of myelin basic protein (MBP) as part of a modified MHC class II construct of the invention (Example 5, pages 50-57 in particular). The rats are immunized either with the peptide itself or with intact MBP in order to induce EAE. Rats in the treatment group are given the MHC class II construct starting at day 3 after the injection of the inducing antigen (page 52 in particular) and boosted several times thereafter. However, it is well

known in the art that there is a latency period between the injection of antigen and the appearance of EAE symptoms in the rat of about 10 days, as evidenced by Besong et al (page 5406, column 1 through page 5047, column 1 in particular; J. Neurosci. [2002] 22(13):5403-5411; W on form PTO-892, newly cited for evidentiary purposes). Accordingly, the first treatment dose is administered well before the onset of symptoms and likely before epitope spreading becomes an issue.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 37-40, 54, and 59-82 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

3. No claim is allowed.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
January 8, 2007

David A. Saunders

DAVID A. SAUNDERS
PRIMARY EXAMINER